



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

Address: COMMISSIONER FOR PATENTS

P.O. Box 1450

Alexandria, Virginia 22313-1450

www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,608	12/05/2005	Michal Hock	4367-0107PUS1	3490
2292 7590 01/30/2008 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747				
EXAMINER				
BERCH, MARK L				
ART UNIT		PAPER NUMBER		
1624				
NOTIFICATION DATE		DELIVERY MODE		
01/30/2008		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

# Office Action Summary

**Application No.**

10/537,608

**Applicant(s)**

HOCEK ET AL.

**Examiner**

/Mark L. Berch/

**Art Unit**

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SF/88)  
Paper No(s)/Mail Date 06/03/2005
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_

### DETAILED ACTION

#### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-4, are rejected under 35 U.S.C. 102(b) as being anticipated by Chaman (1963).

See the Table, compounds XVII, XVI, XVIII, which correspond to R2 as H, Cl or OH, R1 as H, R as NH<sub>2</sub>, m=0, Ym as methylene.

Claims 1, 3-4, are rejected under 35 U.S.C. 102(b) as being anticipated by Chaman (1966).

See compound III R2 as dimethylamino, R1 as H, R as NH<sub>2</sub>, m=0, Ym as methylene.

Claims 1, 3-4, are rejected under 35 U.S.C. 102(b) as being anticipated by Woenckhaus.

See compound prepared, R1 as H, R as NH<sub>2</sub>, m=0, Ym as methylene. It differs from above species in having R4 as H rather than methyl.

#### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The compound of Formula 2, and the product of claim 9, does not fall within Formula I. It represents a situation where R' and R" combine to form a protecting group. This is not provided for in Formula I. Thus, either Formula I is misdrawn, or the structure in Claim 2 and claim 9 is misdrawn (i.e. wrongly has the = present). It is impossible to tell which is which.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This case was filed without an adequate teaching of utility. The specification teaches "pharmaceutical product such as an anticancer agent, an antiviral agent and the like, a production intermediate therefor". In view of the fact that there are hundreds of cancers, and thousands of viruses, this amounts to no more than a teaching for the public to figure out for themselves how to use. That will not suffice. As was stated in *In re Gardner, Roe, and Willey*, 166 USPQ 138 at 141 (CCPA 1970), "In other words, those skilled in the art, by investigations along the above lines, and by a great amount of work, can eventually find out how to use appellants' invention. But our view is that the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves." It will take undue experimentation to figure out how to use.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction

Art Unit: 1624

provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is “undue”; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the extremely wide range of R1, R2, R3 and R4 the A-linker, trillions of compounds are embraced.

(b) Scope of the diseases covered. The coverage of “anticancer ... antiviral “is immense. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body. Here are some assorted categories:

A. CNS cancers cover a very diverse range of cancers in many categories and subcategories. There are an immense range of neuroepithelial tumors. Gliomas, the most common subtype of primary brain tumors, most of which are aggressive, highly invasive, and neurologically destructive tumors are considered to be among the deadliest of human cancers. These are any cancers which show evidence (histological, immunohistochemical, ultrastructural) of glial differentiation. These fall mostly into five categories. There are the astrocytic tumors (Astrocytomas): Pilocytic astrocytoma (including juvenile pilocytic astrocytoma, JPA, and pediatric Optic Nerve Glioma) Diffuse astrocytomas (including Fibrillary astrocytomas, Protoplasmic astrocytomas and Gemistocytic astrocytomas), Anaplastic astrocytomas (including adult Optic Nerve Glioma), Glioblastoma multiforme (GBM), gliosarcoma and giant cell glioblastoma, and Pleomorphic xanthoastrocytoma. GBM exists in two forms, primary and secondary, which have very different clinical histories and different genetics, but GBM is considered to be one clinical entity. Second, there are the oligodendroglial tumors (Oligodendrogliomas): Low grade Oligodendroglioma and Anaplastic

**Oligodendroglioma.** Third, there is oligoastrocytomas (“mixed glioma”), a type of tumor with both astrocytoma & oligodendroglioma features. The fourth type is the Ependymomas, which are intracranial gliomas, including Papillary Ependymoma, Myxopapillary ependymoma, tanycytic ependymoma, Anaplastic ependymoma and subependymal giant-cell astrocytomas. A fifth type is the Gangliogliomas (glioneuronal tumors or glioneurocytic tumors), which have both glial and neuronal components, and are extremely varied, based in part on what types of glial and what types of neuronal components are present. These include Papillary Glioneuronal Tumor (PGNT), a range of Supratentorial gangliogliomas, assorted intramedullary spinal cord gangliogliomas, Pineal ganglioglioma, Hypothalamic ganglioglioma, cerebellar ganglioglioma, Ganglioglioma of the right optic tract, rosetted glioneuronal tumor (“glioneurocytic tumor with neuropil rosettes”), composite pleomorphic xanthoastrocytoma (PXA)-ganglioglioma, desmoplastic ganglioglioma (both infantile (DIG) and non- infantile), Angioganglioglioma, and others. There are also some Glial tumors which do not comfortably fit into these five categories, notably Astroblastoma, Gliomatosis cerebri, and chordoid glioma, which is found solely in the Hypothalamus and Anterior Third Ventricle. Other neuroepithelial tumors include astrocytic tumors (e.g. astrocytomas) oligodendroglial tumors, Ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus(Choroid plexus papilloma, Choroid plexus carcinoma), assorted neuronal and Neuroblastic tumors (e.g. gangliocytoma, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma, Olfactory neuroblastoma, Olfactory neuroepithelioma, and Neuroblastomas of the adrenal gland), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma, and Pineal parenchymal tumor of intermediate differentiation), embryonal tumors (e.g. medulloepithelioma, neuroblastoma, retinoblastoma, ependymblastoma, Atypical teratoid/rhabdoid tumor, Desmoplastic medulloblastoma, Large cell medulloblastoma,

Medulloblastoma, and Melanotic medulloblastoma) and others such as polar spongioblastoma and Gliomatosis cerebri. A second Division is tumors of the meninges. This includes tumors of the meningeothelial cells, including Meningiomas (Meningothelial, Fibrous (fibroblastic), Transitional (mixed), Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich, Metaplastic, Clear cell, Chordoid, Atypical, Papillary, Rhabdoid, Anaplastic meningioma) and the non- Meningioma tumors of the meningeothelial cells (Malignant fibrous histiocytoma, Leiomyoma, Leiomyosarcoma, Rhabdomyoma, Rhabdomyosarcoma, Chondroma, Chondrosarcoma, Osteoma, Osteosarcoma, Osteochondroma, Haemangioma, Epithelioid haemangioendothelioma, Haemangiopericytoma, Angiosarcoma, Kaposi sarcoma). There are also Mesenchymal, non-meningeothelial tumors (Lipomas, Angiolipoma, Hibernoma Liposarcoma, (intracranial)Solitary fibrous tumor, and Fibrosarcoma) as well as Primary melanocytic lesions (Diffuse melanocytosis, Melanocytoma, Malignant melanoma, and Meningeal melanomatosis). A third Division are the tumors of Cranial and Spinal Nerves. This includes Cellular schwannomas, Plexiform schwannomas and the Melanotic schwannomas (e.g. psammomatous melanotic schwannoma , Neuro-axial melanotic schwannoma, Dorsal dumb-bell melanotic schwannoma). There is also neurofibroma, Perineurioma (Intraneural and Soft tissue) and malignant peripheral nerve sheath tumor (MPNST), including Epithelioid, MPNST with divergent mesenchymal differentiation, and MPNST with epithelial differentiation. A fourth division are Germ Cell Tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma (Mature teratoma, Immature teratoma, and Teratoma with malignant transformation). A fifth division are the tumors of the Sellar Region, viz. pituitary adenoma, pituitary carcinoma, granular cell myoblastoma and craniopharyngiomas (Adamantinomatous and Papillary). Yet another division are local extensions from regional tumors, including paraganglioma, chondroma, chordoma, and chondrosarcoma. There are also Primitive Neuroectodermal Tumors (PNETs) including

Medulloblastomas, medulloepitheliomas, ependymoblastomas and polar spongioblastomas. There are Vascular brain Tumors e.g. the hemangioblastomas, there is CNS Lymphoma (which can be primary or secondary) and Meningeal Carcinomatosis. There are Lymphoma AND Haemopoietic neoplasms including Malignant lymphomas (which can be primary or secondary), Plasmacytoma, and Granulocytic sarcoma. And there are many, many others.

B. Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These includes viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia (HCL, a chronic Lymphoid leukemia). There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, adult T cell leukemia/lymphoma (ATLL), and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias (undifferentiated AML, acute myeloblastic, acute myelomonocytic leukemia, acute monocytic leukemias, acute monoblastic, acute megakaryoblastic (AmegL), acute promyelocytic leukemia (APL), and erythroleukemia). There is also lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-/BCR- myeloid leukemia, and acute basophilic leukemia. Chronic leukemias include chronic lymphocytic leukemia (CLL, which exists in a B-cell and a T-cell type), prolymphocytic leukemia (PLL), large granular lymphocytic leukemia (LGLL, which goes under several other



Art Unit: 1624

names as well), chronic myelogenous leukemia(CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, chronic eosinophilic leukemia(CEL), and many others.

C. Carcinomas of the Liver include Hepatocellular carcinoma, Combined hepatocellular cholangiocarcinoma, Cholangiocarcinoma (intrahepatic), Bile duct cystadenocarcinoma and Undifferentiated carcinoma of the liver. There are also two types of liver hemangioma: cavernous and hemangioendothelioma.

D. The main types of lung and pleural cancer are small cell (i.e. oat cell, including combined oat cell), adenocarcinomas, Bronchioloalveolar carcinomas (Nonmucinous, Mucinous, and Mixed mucinous and nonmucinous or indeterminate cell type), Acinar, Papillary carcinoma, Solid adenocarcinoma with mucin, Adenocarcinoma with mixed subtypes, Well-differentiated fetal adenocarcinoma, Mucinous (colloid) adenocarcinoma, Mucinous cystadenocarcinoma, Signet ring adenocarcinoma, and Clear cell adenocarcinoma), squamous cell (Papillary, Clear cell, Small cell and Basaloid), mesothelioma (including epithelioid, sarcomatoid, desmoplastic and biphasic) and Large Cell Carcinoma (which include Large-cell neuroendocrine carcinoma, Combined large-cell neuroendocrine carcinoma, Basaloid carcinoma, Clear cell carcinoma Lymphoepithelioma-like carcinoma, and Large-cell carcinoma with rhabdoid phenotype). In addition there are also the carcinomas with pleomorphic, sarcomatoid or sarcomatous elements, including Carcinomas with spindle and/or giant cells, Spindle cell carcinoma, Carcinosarcoma and Pulmonary blastoma. The non-small cell lung carcinomas also include Adenosquamous carcinoma, the Carcinoid tumor (both typical Carcinoid and atypical Carcinoid) as well as carcinomas of salivary-gland type, including mucoepidermoid carcinoma and adenoid cystic carcinoma. There are some soft tissue tumors including localized fibrous tumor (formerly called benign fibrous mesothelioma); epithelioid haemangioendothelioma; pleuropulmonary blastoma; chondroma; calcifying fibrous pseudotumor of the visceral pleura); congenital peribronchial myofibroblastic tumors, diffuse pulmonary

lymphangiomyomatosis and desmoplastic round cell tumor. There are assorted bronchial adenomas (eg, adenoid cystic carcinomas, mucoepidermoid carcinomas, mucous gland adenomas, and oncocytomatous bronchial mucous gland adenoma) as well as other adenomas, including papillary adenoma. There are some papillomas, including squamous cell papilloma and glandular papilloma. There is also malignant melanoma of the lung, Hamartoma, cylindroma (cylindroadenoma), some germ cell tumors, thymoma and sclerosing haemangioma and many others as well.

E. Thyroid cancer comes in four forms: papillary thyroid cancer, follicular thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer.

F. Carcinomas of the skin are the Basal cell carcinomas (BCC), including Superficial BCC, Nodular BCC (solid, adenoid cystic), Infiltrating BCC, Sclerosing BCC (desmoplastic, morpheic), Fibroepithelial BCC, BCC with adnexal differentiation, Follicular BCC, Eccrine BCC, Basosquamous carcinoma, Keratotic BCC, Pigmented BCC, BCC in basal cell nevus syndrome, Micronodular BCC. Another important family is the Squamous cell carcinomas (SCC) which include Spindle cell (sarcomatoid) SCC, Acantholytic SCC, Verrucous SCC, SCC with horn formation, and Lymphoepithelial SCC, along with less well classified SCCs such as Papillary SCC, Clear cell SCC, Small cell SCC, Posttraumatic (e.g., Marjolin ulcer) and Metaplastic (carcinosarcomatous) SCC. Another family is the Eccrine carcinomas including Sclerosing sweat duct carcinoma (syngomatous carcinoma, microcystic adnexal carcinoma), Malignant mixed tumor of the skin (malignant chondroid syringoma), Porocarcinoma, Malignant nodular hidradenoma, Malignant eccrine spiradenoma, Mucinous eccrine carcinoma, Adenoid cystic eccrine carcinoma, and Aggressive digital papillary adenoma/adenocarcinoma. Other carcinomas of the skin include Epidermal carcinomas, Paget disease, Mammary Paget disease, Extramammary Paget disease Adnexal carcinomas, Apocrine carcinoma, Sebaceous carcinoma, Tricholemmocarcinoma and Malignant pilomatricoma (matrical carcinoma).

Art Unit: 1624

G. There are many types of colon cancers, and this category is rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas (which can be primary or metastatic), sarcomas (including fibrosarcomas and Leiomyosarcomas), and Carcinoid tumors.

H. Renal carcinomas include papillary renal cell carcinoma, conventional-type (clear cell) renal carcinoma, chromophobe renal carcinoma, collecting duct carcinoma, and some unclassified carcinomas. Other kidney cancers include Transitional Cell Carcinoma, Wilms Tumors, and Renal Sarcomas.

I. Prostate Cancer is not a single disease or group of very closely related disorders, but ranges over a very wide variety of cancer types. It embraces various adenocarcinomas of the prostate, including Prostatic Ductal Adenocarcinoma, adenocarcinoma with Paneth-like cells, Clear cell adenocarcinoma, Foamy gland adenocarcinoma, Adenocarcinoma of Cowper's glands, and Atrophic adenocarcinoma. It includes a huge variety of carcinomas, including mucinous carcinomas of the prostate, Prostatic carcinoma of xanthomatous type, signet ring cell carcinoma of the prostate, neuroendocrine small cell carcinoma of the prostate, and other small cell carcinomas of the prostate, Adenosquamous and Squamous Cell Carcinomas, Basaloid and Adenoid Cystic Carcinoma, Sarcomatoid carcinoma of the prostate, Lymphoepithelioma-like Carcinoma of the prostate, Urothelial (transitional Cell) Carcinoma (which can be primary in the prostate gland or represent secondary spread from the urinary bladder), Basaloid carcinoma, pseudohyperplastic carcinoma, and Primary carcinoma of the Seminal vesicles. There are also assorted sarcomas of the prostate, including Angiosarcoma, Embryonal rhabdomyosarcoma, Stromal sarcoma, Synovial sarcoma, Leiomyosarcoma, and chondrosarcoma of the prostate, which can be primary or secondary to the prostate. Also included is prostatic intraepithelial neoplasia (PIN), Phylloides

Art Unit: 1624

**Tumor of the Prostate, Primitive peripheral neuroectodermal tumor (PNET) and Malignant fibrous histiocytoma.** There are also lymphomas, which are usually secondary, but primary ones include **Diffuse Large B-cell Lymphoma**. The great majority of this list are not treatable with pharmaceuticals.

**J. Penile carcinoma** is usually a squamous cell carcinoma, but there is also Penile clear cell carcinoma and Sarcomatoid carcinoma.

**K. The carcinomas of the extrahepatic bile ducts** are of numerous types, including carcinoma in situ, Adenocarcinoma, Papillary adenocarcinoma, Adenocarcinoma (intestinal-type), Mucinous adenocarcinoma, Clear cell adenocarcinoma, Signet ring cell carcinoma, Adenosquamous carcinoma, Squamous cell carcinoma, Small cell carcinoma (oat cell carcinoma) and undifferentiated carcinoma of the extrahepatic bile ducts.

**L. Breast cancers** come in great variety. The most important category of breast cancers is the ductal cancers. These come in a wide variety of types. Presently, these are divided into the following categories: Intraductal (in situ); Invasive with predominant intraductal component; Invasive, NOS; Comedo; Inflammatory (IBC); Medullary with lymphocytic infiltrate; Mucinous Carcinoma (colloid carcinoma); Papillary carcinoma; Scirrhus; Tubular; and Other. Another category is the Lobular breast cancers, which can be in situ, Invasive with predominant in situ component, and Invasive. There is Paget's disease of the Nipple, which can be also with intraductal carcinoma or with invasive ductal carcinoma. There is Adenomyoepithelioma, a dimorphic tumor characterized by the presence of both epithelial and myoepithelial cells. There is breast angiolipoma and spindle cell lipoma of the breast. There is lymphoma of the breast (which exists in both Non-Hodgkin's lymphoma of the breast and Hodgkin's disease of the breast forms). There are some sarcomas, including giant cell sarcoma of the breast, leiomyosarcoma of the breast, Angiosarcoma of the breast, cystosarcoma phylloides, and liposarcoma of the breast. There are carcinoid tumors which

Art Unit: 1624

can be primary carcinoid tumors of the breast, or can arise from nonmammary sources.

There are breast salivary gland-like tumors, including acinic cell carcinoma (AcCC), oncocytic carcinoma (Mammary epithelial oncocytoma), and mucoepidermoid carcinoma (MEC). Other rare carcinomas include Spindle cell carcinoma of the breast (SpCC), Squamous cell carcinoma of the breast, Secretory Carcinoma of the Breast (Juvenile secretory carcinoma), Metaplastic carcinoma of the breast (a heterogeneous group of invasive breast cancers including types with squamous differentiation and those with heterologous elements), Invasive Micropapillary Carcinoma of the Breast, Adenoid cystic carcinoma of the breast, cribriform carcinoma, Myofibroblastoma of the Breast (Benign spindle stromal tumor of the breast) and glycogen-rich clear cell carcinoma of the breast. There are numerous other rare breast cancers, including for example Fibromatosis of the breast (extra-abdominal desmoid), Angiomatosis of the Breast, and mammary hamartoma. There are also nonmammary tumors, primarily adenocarcinomas, that can metastasize to the breast including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas, and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus, and colon).

M. Ovarian cancers are a heterogeneous group of tumors. The most important are the epithelial tumors. These are themselves fairly diverse, the categories being Serous cystomas (Serous benign cystadenomas, Serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth and Serous cystadenocarcinomas); Mucinous cystomas (divided the same three ways); Clear cell tumors (mesonephroid tumors, again divided the same way), Endometrioid tumors (similar to adenocarcinomas in the endometrium: Endometrioid benign cysts, Endometrioid tumors with proliferating activity of the epithelial cells and Endometrioid adenocarcinomas), mixed mesodermal (now considered to be carcinomas with

Art Unit: 1624

areas of sarcomatous differentiation), clear cell, transitional cell, and mixed epithelial. Second, there are the Granulosa-Stromal Cell Tumors. These include the Granulosa cell tumor (which exists in juvenile and adult forms) and the tumors in the thecoma-fibroma group. This includes thecoma-fibroma group typical thecoma and luteinized thecoma or "stromal Leydig cell tumor". This also includes fibroma, cellular fibroma, fibrosarcoma, stromal tumor with minor sex cord elements, sclerosing stromal tumor, signet ring cell stromal tumor and others. Third, there are the Sertoli-Leydig Cell Tumors and Androblastomas. These include the Sertoli cell tumor (tubular androblastoma), Sertoli-Leydig cell tumor, a poorly differentiated sarcomatoid, tumor and a Retiform tumor. Fourth, there are some miscellaneous Sex Cord Stromal Tumors, including Gynandroblastoma of the ovary (composed of sex cord and stromal cells of both ovarian and testicular types), Sex Cord Tumor with Annular Tubules, Stromal luteoma, and Leydig cell tumor (which comes in hilus and non-hilus types). Fifth, there are an assortment of Germ Cell Tumors. These include Dysgerminoma; Yolk Sac Tumors (Endodermal Sinus Tumor, and Polyvesicular vitelline tumor, Hepatoid and others); Embryonal Carcinoma; Polyembryoma; Choriocarcinoma and a wide variety of Teratomas. These teratomas include immature, cystic (dermoid cyst), retiform (homunculus), and Monodermal, including struma ovarii, carcinoid (insular and trabecular), struma carcinoid, mucinous carcinoid, neuroectodermal tumors, sebaceous tumors and others. Finally, there are an assortment of other tumors which do not fit into the above categories. There is Gonadoblastoma and Tumors of Rete Ovarii (which can be Adenomatoid tumor or a Mesothelioma). There are some tumors of Uncertain Origin, including Small cell carcinoma, tumors of probable Wolffian origin, a Hepatoid carcinoma and Oncocytoma. There are some Soft Tissue Tumors not Specific to Ovary, and there are assorted malignant Lymphomas and Leukemias which land up in the ovaries.

Art Unit: 1624

N. Cervical cancers. There are many different categories and sub-categories of cervical cancers. The majority of cervical cancers are Squamous Cell Carcinomas. These come in numerous types: large cell nonkeratinizing type; large cell keratinizing type; Basaloid; Verrucous; Warty; Papillary; Lymphoepithelioma-like; and Squamotransitional, Early invasive (microinvasive) squamous cell carcinoma; Squamous intraepithelial neoplasia (including Cervical intraepithelial neoplasia and Squamous cell carcinoma in situ). There are also a variety of Adenocarcinomas, the most important of which are the Mucinous adenocarcinoma, which include the Endocervical, Intestinal, signet-ring cell, minimal deviation, and Villoglandular. There is also Endometrioid adenocarcinoma, clear cell adenocarcinoma, serous adenocarcinoma, Mesonephric adenocarcinoma, Early invasive adenocarcinoma, and Adenocarcinoma in situ. In addition, there are neuroendocrine carcinomas, divided into Small Cell, large cell, classical carcinoid and atypical carcinoid. Other epithelial tumors include Adenosquamous carcinoma, mixed Adenosquamous Carcinomas, which can be either well-differentiated or poorly differentiated, the latter including glassy cell carcinoma, adenoid cystic carcinoma, adenoid basal carcinoma and Undifferentiated carcinoma. There are also some mixed carcinoma with signet-ring cells, and other types of other poorly differentiated mixed carcinomas. This group includes tumors sometimes called apudomas or argyrophil cell carcinomas. There are also an assortment of Mesenchymal tumors of the cervix, including Leiomyosarcoma; Endometrioid stromal sarcoma, low grade; Undifferentiated endocervical sarcoma; Sarcoma botryoides; Alveolar soft part sarcoma, Angiosarcoma of the cervix, Malignant peripheral nerve sheath tumor of the cervix; Cervical leiomyoma; and Rhabdomyoma of the cervix. There are also some mixed epithelial and mesenchymal tumors, including Carcinosarcoma (malignant müllerian mixed tumor), Adenosarcoma, Wilms tumor, typical and atypical Polypoid Adenomyoma, and Papillary adenofibroma of the cervix. There are also Melanocytic tumors, including primary malignant melanoma of the cervix and Blue naevus of

Art Unit: 1624

the cervix. There are also germ cell type tumors, including Yolk sac tumor, Dermoid cyst, and Mature cystic teratoma of the cervix. There is also primary choriocarcinoma of the cervix, which does not fit well into any category. There are also cancers secondary to the cervix, which have spread from elsewhere.

**O. Bladder cancers.** Most cases of bladder cancers are transitional cell (urothelial) carcinoma, which includes non-invasive papillary urothelial carcinoma, Flat urothelial carcinoma in situ (CIS), Superficially invasive urothelial carcinoma, and muscle invasive tumors. Adenocarcinomas of the bladder include Primary Adenocarcinoma (urachal and non-urachal), Prostatic adenocarcinoma, Gastro-intestinal adenocarcinomas and Clear cell carcinoma. Squamous cell carcinomas include Verrucous carcinomas, and a secondary squamous cell carcinoma of the bladder, from the cervix. Small cell carcinomas include Primary small cell carcinoma of the bladder and the secondary small cell carcinoma ('reserve cell carcinoma') of the lung. Lymphomas include the primary lymphomas (Low grade B-cell lymphoma of MALT type, High grade B-cell lymphoma, and T-cell lymphoma), as well as secondary lymphomas, including mantle cell lymphomas. Melanomas include Primary Malignant melanoma of the bladder, and secondary ones. The sarcomas of the Bladder are Leiomyosarcoma, Osteosarcoma and Rhabdomyosarcoma. There is also a primary primitive neuroectodermal tumour (PNET) of the bladder, Paraganglioma (which can metastasize), Nephrogenic adenoma, Metastatic renal cell carcinoma of the bladder, and both primary and secondary (from the uterus) Choriocarcinoma of the bladder.

**P. Cancers of the Vulva** are mostly Squamous carcinoma, but these also include Melanoma, Bartholin's Adenocarcinoma, Basal Cell carcinoma and some Sarcomas.

**Q. Vaginal cancers** are primarily Squamous Carcinoma, but some are Adenocarcinoma, Melanoma of the vagina; Sarcoma of the vagina, Bowen's disease and Germ Cell Tumors.



Art Unit: 1624

**R. The most important of the cancers of the uterus are the Endometrial Carcinomas. The great majority of these are Endometrioid; others include Uterine Papillary Serous Tumor (UPST), Clear Cell Carcinoma, Mucinous and Squamous. Uterine Sarcomas include Smooth Muscle Tumors include leiomyoblastoma, clear cell leiomyoma, epithelioid leiomyoma, plexiform tumorlet, Intravenous leiomyomatosis, Benign metastasizing leiomyoma, Leiomyomatosis peritonealis disseminate and Leiomyosarcoma (LMS). Endometrial Tumors include Endometrial stromal nodule, Endolymphatic stromal myosis, (ESM) and Endometrial stromal sarcoma (ESS). There are the mixed tumors Müllerian adenosarcoma and Malignant mixed mesodermal tumors (MMMT). Other sarcomas are Rhabdosarcoma, Osteosarcoma, Chondrosarcoma nad Hemangiopericytoma. There are also uterine cancers which do not come from uterine cells themselves, but start in the tissue that begins to develop immediately after conception: Persistent gestational trophoblastic disease, choriocarcinoma and placental site trophoblastic tumors (PSTT).**

**S. There are several main types of stomach cancers, which are very different from each other. (1) Lymphomas of the stomach are cancers of the immune system tissue that are found in the wall of the stomach. These come in two main categories. One is the Non-Hodgkin's lymphomas of the stomach, including MALT lymphoma, and assorted Large Cell Lymphoma of the Stomach such as anaplastic CD30 (Ki-1) positive large cell lymphoma (ALCL). The other is Hodgkin Lymphoma in the Stomach. These include both lymphomas which are primary to the stomach, and nodal lymphomas that have spread to the stomach from e.g. the spleen or liver and are thus secondary. There are Tertiary gastric lymphomas as well. (2) Gastric stromal tumors (GISTs) develop from the tissue of the stomach wall. There are an assortments of these; GISTs vary from cellular spindle cell tumors to epithelioid and pleomorphic ones. (3) Carcinoid tumors are tumors of hormone-producing cells of the stomach. These are classified into are classified into those that are associated with hypergastrinemic states (type 1, atrophic gastritis, pernicious anemia); Zollinger-Ellison**

Art Unit: 1624

syndrome [ZES] tumors (type 2), and tumors without hypergastrinemia (type 3 or sporadic). (4) Carcinoma of the Stomach exists in five types: papillary, tubular, mucinous, signet-ring cell adenocarcinoma and undifferentiated carcinoma. (5) Soft tissue sarcomas, most notably leiomyosarcoma of the stomach. There are other tumors as well, including Gastric Lipoma, gastric xanthelasma, and benign reactive lymphoid hyperplasia (pseudolymphoma).

In addition there are viruses. This is an immense category of diverse viruses. Arenaviridae (the arenaviruses, Negative Stranded ssRNA) have considerable diversity. These are divided into two serogroups, the "Old World" and the "New World". The Old World includes the Ippy virus, Lassa virus (including different strains GA391 virus and Josiah virus), and Lymphocytic choriomeningitis virus (LCMV) (including several different strains of Armstrong virus as well as the WE virus). It also includes the Mobala virus and the Mopeia virus, each with multiple strains. The New World arenaviruses include Amapari virus, Flexal virus, Guanarito virus, Junín virus, Latino virus, Machupo virus, Oliveros virus, Paraná virus, Pichinde virus, Pirital virus, Sabiá virus, Tacaribe virus, Tamiami virus, and Whitewater Arroyo virus. Again, many have multiple strains. These viruses are not necessarily closely related even within the same serogroup. For example, based on sequence data Pichinde virus appears to diverge quite extensively from the Tacaribe, Machupo, Junín, even though all 4 are New World. And the strains of LCMV (a virus actually found in Africa, Europe and the Americas) are only distantly related to the African viruses.

There is also the Filoviridae (Negative Stranded ssRNA), which consists of the Marburg virus (which has 6 different strains), and the Ebola virus (which has 4 different strains).

The Bunyaviridae Family (Negative Stranded ssRNA) is immense, with several genera, including the Orthobunyavirus, Hantavirus, Nairovirus, and Phlebovirus. It includes the Acara virus, Akabane virus, Alajuela virus, San Juan virus, Anopheles B virus, Bakau virus, Batama

Art Unit: 1624

virus, Birao virus, Bozo virus, Cache Valley virus, Fort Sherman virus, Germiston virus, Iaco virus, Mboke virus, Ngari virus, Northway virus, Bwamba virus, Capim virus, Caraparu virus, Catu virus, Estero Real virus, Gamboa virus, Guajara virus, Guama virus, Madrid virus, Manzanilla virus, Minatitlan virus, Nyando virus, Olifantsvlei virus, Oriboca virus, Sathuperi virus, Shuni virus, Tacaiuma virus, Wyomyia virus, Kaeng Khoi virus, Andes virus, Bayou virus, Black Creek Canal virus, Cano Delgadito virus, Dobrava-Belgrade virus, Muleshoe virus, Puumala virus, Rio Mamore virus, Thailand virus, Topografov virus, Tula virus, Crimean-Congo hemorrhagic fever virus, Dugbe virus, Qalyub virus, Bujaru virus, Punta Toro virus, Rift Valley fever virus, Salehebad virus, Sandfly fever Naples virus, Uukuniemi virus, Gabek Forest virus, Sandfly fever Sicilian virus and dozens more. Many of these have numerous different strains which have been identified. The family includes numerous viruses that are so poorly understood that it is impossible to place them in one of the above genres, such as Bangui virus, Witwatersrand virus, and Kowanyama virus.

The human Flavivirus (Positive Stranded ssRNA Virus) are a diverse lot, including the Pestiviruses (such as Classical swine fever (CSF) and Bovine viral diarrhoea / Mucosal disease (BVD/MD)), Hepatitis C, Yellow fever virus, Gadgets Gully virus, Kadam virus, Kyasanur Forest disease virus, Langat virus, Omsk hemorrhagic fever virus, Powassan virus, Royal Farm virus, Tick-borne encephalitis virus, Meaban virus, Tyuleny virus, Aroa virus, Dengue virus, Kedougou virus, Cacipacore virus, Koutango virus, Japanese encephalitis virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Usutu virus, West Nile virus, Kunjin virus, Ntaya virus, Uganda S virus, Apoi virus, Montana myotis leukoencephalitis virus, and many, many more.

The reoviruses (dsRNA Virus) have 12 genera. The Orthoreovirus includes the Mammalian orthoreovirus, Avian orthoreovirus, Nelson Bay orthoreovirus, and Baboon orthoreovirus, all with multiple strains, along with the Python orthoreovirus, Rattlesnake orthoreovirus Ndelle virus

Art Unit: 1624

and the Duck reovirus. The Orbivirus includes the African horse sickness virus, Bluetongue virus, Epizootic hemorrhagic disease virus, Equine encephalosis virus, all with many strains, along with the Altamira virus (ALTV), Caninde virus (CANV), Changuinola virus (CGLV), Gurupi virus (GURV), Irituia virus (IRIV), Jamaxi virus (JAMV), Jari virus (JARIV), Monte Dourado virus (MDOV), Ourem virus (OURV), Purus virus (PURV), Saraca virus, Baku virus (BAKUV), Chenuda virus (CNUV), Essaouira virus (ESSV), Huacho virus (HUAV), Kala Iris (KIRV), Mono Lake virus (MLV), Sixgun city virus (SCV), Chobar Gorge virus (CGV), Fomede virus, Acado virus (ACDV), Corriparta virus CS109, Corriparta virus V654, Corriparta virus V370, Jacareacanga virus, Above Maiden virus, Arbroath virus (ABRV), Bauline virus (BAUV), Broadhaven virus (BRDV), Cape Wrath virus (CWV), Colony virus (COYV), Colony B North virus, Ellidaey virus (ELLV), Foula virus (FOUV), Great Island virus (GIV), Great Saltee Island virus (GSIV), Grimsey virus (GSYV), Inner Farne virus (INFV), Kemeroovo virus (KEMV), Kenal virus (KENV), Kharagysh virus (KHAV), Lipovnik virus (LIPV), Lundy virus (LUNV), Maiden virus (MDNV), Mill Door virus (MDRV), Mykines virus (MYKV), North Clett virus (NCLV), North End virus (NEDV), Nugget virus (NUGV), Okhotskiy virus (OKHV), Poovoot virus (POOV), Rost Island virus (RSTV), St Abb's Head virus (SAHV), Shiant Islands virus (SHIV), Thormodseyjarlettur virus (THRV), Tillamook virus, Tindholmur virus (TDMV), Tribec virus (TRBV), Vearoy virus (VAEV), Wexford virus (WEXV), Yaquina Head virus (YHV), Wexford virus (WEXV), Lebombo virus 1 (LEBV), Orungo virus, Abadina virus (ABAV), Bunyip creek virus (BCV), CSIRO village virus (CVGV), D'Aguilar virus (DAGV), Kasba virus (KASV), Chuzan virus, Kindia virus (KINV), Marrakai virus (MARV), Nyabira virus (NYAV), Palyam virus (PALV), Petevo virus (PETV), Vellore virus, Llano Seco virus (LLSV), Minnal virus (MINV), Netivot virus (NETV), Umatilla virus (UMAV), Wad Medani virus, Seletar virus, Mudjinbarry virus (MUDV), Wallal virus (WALV), Wallal K virus, Mitchell River virus (MRV), Warrego virus

Art Unit: 1624

(WARV), Warrego K virus, Paroo River virus (PRV), Picola virus (PIAV), Wongorr virus MRM1343, Wongorr virus CSI31, Wongorr virus V195, Wongorr virus V199, Wongorr virus V595, Wongorr virus V1447, Andasibe virus, Codajas virus (COV), Ife virus (IFEV), Itupiranga virus (ITUV), Japanaut virus (JAPV), Kammavanpettai virus (KMPV), Lake Clarendon virus (LCV), Matucare virus (MATV), Peruvian horse virus (PHV), Peruvian rodent virus (PC21) (PRV), St Croix River virus (SCRV), Tembe virus (TMEV) and Tracambe virus. The rotoviruses are divided in to 7 species, Rotovirus A-G. The Coltivirus has Colorado tick fever virus and Eyach virus. The Seadornavirus has the Banna virus, Kadipo virus, each with many strains. The Aquareovirus has American oyster reovirus, Angel fish reovirus, Atlantic salmon reovirus, Chinook salmon reovirus DRC, Chum salmon reovirus CS, Masou salmon reovirus, Smelt reovirus, Striped bass reovirus, Chinook salmon reovirus B, Chinook salmon reovirus ICR, Chinook salmon reovirus LBS, Chinook salmon reovirus YRC, Coho salmon reovirus CSR, Coho salmon reovirus ELC, Coho salmon reovirus SCS, Golden shiner reovirus, Grass carp reovirus, Aquareovirus D (ARV-D), Channel catfish reovirus, Aquareovirus E (ARV-E), Turbot reovirus, Aquareovirus F (ARV-F), Chum salmon reovirus PSR, Coho salmon reovirus SSR, Chub reovirus (CHRV), Goldenide reovirus (GIRV), Hard clam reovirus (HCRV), Landlocked salmon reovirus (LSRV), and Tench reovirus (TNRV). The Cypoviruses include Bombyx mori cypovirus 1, Dendrolimus punctatus cypovirus 1, Dendrolimus spectabilis cypovirus 1, Lymantria dispar cypovirus 1, Aporophyla luteola cypovirus 10, Heliothis armigera cypovirus 11, Heliothis zea cypovirus 11, Lymantria dispar cypovirus 11, Mamestra brassicae cypovirus 11, Pectinophora gossypiella cypovirus 11, Pseudaletia unipuncta cypovirus 11, Spodoptera exempta cypovirus 11, Spodoptera exigua cypovirus 11, Autographa gamma cypovirus 12, Mamestra brassicae cypovirus 12, Pieris rapae cypovirus 12, Spodoptera exempta cypovirus 12, Polistes hebraeus cypovirus 13, Heliothis armigera cypovirus 14 A strain, Lymantria dispar cypovirus 14, Trichoplusia ni cypovirus 15,

Art Unit: 1624

*Trichoplusia ni* cytoplasmic polyhedrosis virus 15, *Choristoneura fumiferana* cypovirus 16, *Aglais urticae* cypovirus 2, *Agraulis vanillae* cypovirus 2, *Arctia caja* cypovirus 2, *Arctia villica* cypovirus 2, *Boloria dia* cypovirus 2, *Boloria dia* cypovirus 2, *Dasychira pudibunda* cypovirus 2, *Eriogaster lanestris* cypovirus 2, *Hyloicus pinastri* cypovirus 2, *Inachis io* cypovirus 2, *Lacanobia oleracea* cypovirus 2, *Malacosoma neustria* cypovirus 2, *Mamestra brassicae* cypovirus 2, *Operophtera brumata* cypovirus 2, *Papilio machaon* cypovirus 2, *Phalera bucephala* cypovirus 2, *Pieris rapae* cypovirus 2, *Anaitis plagiata* cypovirus 3, *Arctia caja* cypovirus 3, *Danaus plexippus* cypovirus 3, *Gonometa rufibrunnea* cypovirus 3, *Malacosoma neustria* cypovirus 3, *Operophtera brumata* cypovirus 3, *Phlogophora meticulosa* cypovirus 3, *Pieris rapae* cypovirus 3, *Spodoptera exempta* cypovirus 3, *Actias selene* cypovirus 4, *Antheraea assamensis* cypovirus 4, *Antheraea mylitta* cypovirus 4, *Antheraea pernyi* cypovirus 4, *Antheraea proylei* cypovirus 4, *Euxoa scandens* cypovirus 5, *Heliothis armigera* cypovirus 5, *Orgyia pseudotsugata* cypovirus 5, *Spodoptera exempta* cypovirus 5, *Trichoplusia ni* cypovirus 5, *Aglais urticae* cypovirus 6, *Agrochola helvolva* cypovirus 6, *Agrochola lychnidis* cypovirus 6, *Anaitis plagiata* cypovirus 6, *Anti xanthomista* cypovirus 6, *Biston betularia* cypovirus 6, *Eriogaster lanestris* cypovirus 6, *Lasiocampa quercus* cypovirus 6, *Mamestra brassicae* cypovirus 7, *Noctua pronuba* cypovirus 7, *Abraxas grossulariata* cypovirus 8, *Heliothis armigera* cypovirus 8, *Malacosoma dissitria* cypovirus 8, *Nudaurelia cytherea* cypovirus 8, *Phlogophora meticulosa* cypovirus 8, *Spodoptera exempta* cypovirus 8, *Agrotis segetum* cypovirus 9, *Heliothis armigera* cypovirus B strain (HaCPV-B), *Maruca vitrata* cypovirus (A strain) (MvCPV-A), *Maruca vitrata* cypovirus (B strain) (MvCPV-B), and *Plutella xylostella* cypovirus (PxCPV). The Idnoreoviruses are *Diadromus pulchellus idnoreovirus-1*, *Diadromus pulchellus reovirus*, *Hyposoter exiguae idnoreovirus-2*, *Hyposoter exiguae reovirus*, *Housefly virus*, *Musca domestica idnoreovirus-3*, *Musca domestica reovirus*, *Dacus oleae idnoreovirus-4*, *Dacus oleae reovirus*, *Ceratitis capitata 1 virus*, *Ceratitis capitata idnoreovirus-5*, *Ceratitis 1 virus*,

Art Unit: 1624

*Drosophila* F virus, *Drosophila melanogaster* idnoreovirus-5 and *Drosophila* S virus (DSV). The Fijiviruses include *Galla fijiensis* virus, *Saccharum* virus 2, Sugarcane Fiji disease virus, Garlic dwarf virus (GDV), Cereal tillering disease virus, Nanismo ruvido del mais, Mal de Rio Cuarto virus (MRCV), *Nilaparvata lugens* reovirus (NLRV), *Arrhenatherum* blue dwarf virus, *Lolium* enation virus, Pangola stunt virus (PaSV), and Rice black streak virus. The Phytoreoviruses include *Ine ishuku-byo*, *Oryza* virus 1, Rice mosaic virus, Rice stunt virus, Rice gall dwarf virus (RGDV), *Aureogenus magnivena* virus, Clover big vein virus, Clover wound tumor virus, *Trifolium* virus nervicrassans, *Homalodisca vitripennis* phytoreovirus, and Tobacco leaf enation phytoreovirus (TLEP). The Orzaviruses are the *Echinochloa* ragged stunt virus (ERSV) and the Rice ragged stunt virus (RRSV) which comes in many subtypes, and *Cimex lactularius* reovirus (CIRV), *Macropipus depurator* P reovirus (MdRV-P), *Carcinus mediterraneus* W2 virus (CcRV-W2), *Porcello dilatatus* reovirus (PdRV), and *Buthus occitanus* reovirus. The Mycoreoviruses include *Cryphonectria parasitica* mycoreovirus-1, *Cryphonectria parasitica* reovirus 9B21, *Cryphonectria parasitica* mycoreovirus-2, *Rosellinia* anti-rot virus, and *Rosellinia necatrix* mycoreovirus-3/W370.

The retroviruses (ssRNA RT-Viruses) fall into seven different genres. The first is Alpharetrovirus. These include the Avian leukosis virus (ALV) (which comes in two strains), Rous sarcoma virus (RSV), which has 3 strains, Avian carcinoma Mill Hill virus 2, Avian myeloblastosis virus, Avian myelocytomatosis virus 29, Avian sarcoma virus CT10, Fujinami sarcoma virus, UR2 sarcoma virus (also known as University of Rochester virus 2 and Avian sarcoma virus UR-2), and the Y73 sarcoma virus. The second genus is the Betaretrovirus. This include the Langur virus (LNGV), Mason-Pfizer monkey virus (which comes in 3 strains), Mouse mammary tumor virus, Ovine pulmonary adenocarcinoma virus, Jaagsiekte sheep retrovirus, and the Squirrel monkey retrovirus. The third genus is the Gammaretrovirus. This includes the Feline leukemia virus, Gibbon ape leukemia virus, Guinea pig type C oncovirus, Murine leukemia virus

Art Unit: 1624

(which exists in at least 6 strains and isolates), Porcine type C oncovirus, Finkel-Biskis-Jinkins murine sarcoma, Gardner-Arnstein feline sarcoma virus, Hardy-Zuckerman feline sarcoma virus, Harvey murine sarcoma virus, Kirsten murine sarcoma virus, Moloney murine sarcoma virus, Snyder-Theilen feline sarcoma virus, Woolly monkey sarcoma virus, Viper retrovirus, Chick syncytial virus, Reticuloendotheliosis virus, and the Trager duck spleen necrosis virus. The fourth genus is the Deltaretrovirus. This includes the Bovine leukemia virus, Primate T-lymphotropic virus 1, Human T-lymphotropic virus 1 (HTLV-1), Simian T-lymphotropic virus 1 (STLV-1), Primate T-lymphotropic virus 2 (PTLV-2), Human T-lymphotropic virus 2 (HTLV-2), Simian T-lymphotropic virus 2 (STLV-2), and the Primate T-lymphotropic virus-3. The fifth genus is the Epsilonretrovirus. These include the Walleye dermal sarcoma virus, Walleye epidermal hyperplasia virus type 1, Walleye epidermal hyperplasia virus type 2, Perch hyperplasia virus, and the Snakehead retrovirus. The sixth Genus is the Lentivirus. This includes Bovine immunodeficiency virus, Equine infectious anemia virus, Feline immunodeficiency virus, Feline immunodeficiency virus (Oma), Puma lentivirus, Caprine arthritis encephalitis virus, Visna/maedi virus (which comes in 3 strains), Human immunodeficiency virus 1 (HIV-1, which comes in many strains), HIV-2, HIV-3, and Simian immunodeficiency virus (SIV) which comes in many strains, including African green monkey, chimpanzee SIV, mandrill SIV and others. The seventh genus is the Spumavirus. This includes Bovine foamy virus, Chimpanzee foamy virus, Feline foamy virus, Simian foamy virus 1 and Simian foamy virus 3.

The above list is just a very small fraction of the actual list of known RNA viruses. There are an even larger number of DNA viruses.

The specification also refers to use an intermediate, but since the specification does not say what the compounds are an intermediate for, this is of no value.



Art Unit: 1624

(2) The nature of the invention and predictability in the art: With specific reference to cancer, *Ex parte Kranz*, 19 USPQ2d 1216, 1219 notes the “general unpredictability of the field [of] ...anti-cancer treatment.” *In re Application of Hozumi et al.*, 226 USPQ 353 notes the “fact that the art of cancer chemotherapy is highly unpredictable”. More generally, the invention is directed toward medicine and is therefore physiological in nature. It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved,” and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: None is provided. No cancer or virus is named. The dosage range information is entirely absent.

(4) State of the Prior Art: The claimed compounds are novel, or are anticipated only by species having no utility. Moreover, the compound tend to have structural feature no generally present in antiviral or anticancer compounds. For example, R4 is H or organic group. The simplest organic groups are alkyls. So far as the examiner is aware, there is no effective antiviral or anticancer purine with this 9-alkyl feature. The simplest linker at the 6-position would be an alkylene chain (or a bond), giving an alkanolic acid or ester substituted by an amino group at the 6-position. So far as the examiner is aware, there are no antiviral or anticancer purines with an alkanolic acid or ester either unsubstituted or substituted by anything at the 6-position. Similarly, the examiner notes that R2 and R2 can be alkyl. Again, compounds with such features are simply not seen. Indeed, there are a very small number of purines which have actually been shown to be effective antivirals. So far as the examiner is aware, not a single one has a Carbon atom attached to the 6-position.

(5) Working Examples: There are none. There is no biological data of any kind.

Art Unit: 1624

(6) Skill of those in the art: The prior art knows that there never has been a compound capable of treating cancer generally. "The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally."

(<<http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm#7>> ENABLEMENT DECISION TREE, Example F, situation 1) There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. This is because it is now understood that there is no "master switch" for cancers generally; cancers arise from a bewildering variety of differing mechanisms. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (an estimated at least 20% are of viral origin e.g. EBV, HHV-8, HTLV-1 and other retroviruses), exposure to chemicals such as tobacco tars, genetic disorders (e.g. Tuberous Sclerosis), ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Cancers that affect just a certain type of structure can be quite varied. Fibromas for example include Infantile myofibromatosis, Fibrous hamartoma of infancy. Juvenile hyaline fibromatoses. Infantile digital fibromatoses. Calcifying aponeurotic fibromas. Giant cell fibroblastoma. Ovarian fibroma, Dermatofibroma, myofibroma, myofibromatosis, desmoplastic fibroma, neurofibroma, peripheral odontogenic fibroma, peripheral ossifying fibroma, giant cell fibroma, Chondromyxoid Fibroma, Oral Neurofibroma, Juvenile aponeurotic fibroma (JAF), aggressive infantile fibromatosis (AIF), omental fibroma, Perifollicular fibroma, ameloblastic fibroma, Premalignant Fibroepithelial Tumor (Pinkus Tumor), Periungual fibroma (Koenen tumor), desmoid tumor, tracheal fibroma and many others. Since it is beyond the

Art Unit: 1624

skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are a few cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. One skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. With regard to gliomas, GBM is considered untreatable; no effective agents have emerged for the treatment of GBM, despite 20 years of enrolling patients in clinical trials. It is radiation and surgery which are used for low grade gliomas (e.g. Pilocytic astrocytoma and Diffuse astrocytomas), as no drug has been found effective. There is no drug treatment established as effective for optic nerve gliomas or gangliogliomas. Indeed, very few gliomas of any type are treated with pharmaceuticals; it is one of the categories of cancer that is the least responsive to drugs. Cartilage tumors do not respond to chemotherapy, nor do Cancerous teratomas. Of the thyroid cancers, only one (anaplastic thyroid cancer) can be treated with anticancer agents. The other are treated with radioactivity, surgery, or thyroid suppression hormones. Lymphomas of the stomach are not commonly treated with ordinary anti-cancer agents, but instead, surgery or radiation and antibiotic therapy (e.g. amoxicillin, metronidazole, bismuth, omeprazole) are the Primary Treatments. Neuroendocrine tumors of the cervix generally do not respond to chemotherapy. Renal cell carcinoma does not respond to chemotherapy. A number of sarcomas,

Art Unit: 1624

including Alveolar soft part sarcoma (ASPS), retroperitoneal sarcoma, most liposarcomas, and the assorted chondrosarcomas, are generally considered not to respond to chemotherapy; no chemotherapeutic agent has been established as effective. Aggressive NK cell leukemia is considered to be untreatable with pharmaceuticals. Many cerebral metastases, such as those from non-small-cell lung cancer and melanoma, are not chemosensitive and will not respond to chemotherapy. Hepatocellular Carcinoma is, in humans, possibly the most prevalent solid tumor. Despite strenuous efforts over a period of decades, no chemotherapeutic agent has ever been found effective against this cancer.

Much the same is true for viruses. One of ordinary skill in the art knows that these viruses, and their polymerases, are quite diverse. Viruses exhibit huge variations in their nature. Some virions consist of just a capsid, some of just a nucleocapsid. Some consists of an envelope and a nucleocapsid, and some of an envelope and a core. Some virions consist of an envelope, a nucleocapsid, and a nucleoid. Other virions consist of an envelope, a matrix protein, a nucleoprotein complex, a nucleocapsid, and a polymerase complex, and there are many other forms as well.

The nucleic acids vary considerably as well. In some, the genome is segmented and consists of three segments of circular, negative-sense, single-stranded and double-stranded RNA. In others, the genome is segmented and consists of eight segments of, negative-sense, single-stranded RNA. In others, the genome is not segmented and contains a single molecule of linear positive-sense, single-stranded RNA, or linear double-stranded RNA. In still others, the genome is monomeric, segmented and consists of ten segments of linear double-stranded RNA. In others, the genome consists of three segments of linear, double-stranded RNA. Some genomes are dimeric. Some have non-genomic nucleic acid, some don't. There are many, many other forms. There can be great variation even in the number of nucleotides present.

The viral polymerases are diverse, and include some forms which can use RNA as a template instead of DNA, a type known as RNA dependent RNA polymerases (RDRPs). This type is seen in e.g. some positive strand RNA viruses. The best known RDRPs are polioviral 3Dpol, vesicular stomatitis virus L, and hepatitis C virus NS5b protein.

Unlike in the bacterial area, broad based antivirals are unknown. Even a viral agent against a family such as the Arenaviridae or the Bunyaviridae is unknown; these viruses are simply too diverse. The vast majority of viruses have no effective antiviral treatment.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1, 3, 6 and 4, the quantity of experimentation needed is expected to be great.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Mark L. Berch/ whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1624

**Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.**

**/Mark L. Berch/  
Primary Examiner  
Art Unit 1624**

**1/28/2008**